Effects of Conjugated Equine Estrogen on Health-Related Quality of Life in Postmenopausal Women With Hysterectomy

Results From the Women's Health Initiative Randomized Clinical Trial

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Background: The Women's Health Initiative (WHI) clinical trial of conjugated equine estrogens (CEEs), involving 10 739 postmenopausal women with hysterectomy, aged 50 to 79 years, was stopped early owing to lack of overall health benefit and increased risk of stroke. Because CEE is still prescribed for treatment of menopausal symptoms and prevention of osteoporosis, it is important to understand the overall impact of this therapy on health-related quality of life (HRQOL).

Methods: All participants completed 6 specific measures of quality of life at baseline and 1 year, and a subsample (n=1189) also completed the questions 3 years after randomization. Changes in scores were analyzed for treatment effect.

Results: Randomization to CEE was associated with a statistically significant but small reduction in sleep disturbance at year 1 compared with baseline (mean benefit, 0.4 points on a 20-point scale) and a statistically significant but small negative effect on social functioning (mean effect, −1.3 points on a 100-point scale). There were no significant improvements due to CEE in the areas of general health, physical functioning, pain, vitality, role functioning, mental health, depressive symptoms, cognitive function, or sexual satisfaction at year 1. A subgroup examined 3 years after baseline had no significant benefits for any HRQOL outcomes. Among women aged 50 to 54 years with moderate to severe vasomotor symptoms at baseline, CEE did not improve any of the HRQOL variables at year 1.

Conclusion: In this trial of postmenopausal women with prior hysterectomy, oral CEE did not have a clinically meaningful effect on HRQOL.

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RESULTS OF RECENTLY PUB-lished large, randomized clinical trials have failed to support protective effects of oral estrogen therapy alone or estrogen plus progestin therapy on cardiovascular disease when administered to postmenopausal women.[1-3] Findings of the Women's Health Initiative (WHI)[4] demonstrated that, compared with placebo, women taking conjugated equine estrogens (CEEs) were at increased risk for stroke and deep vein thrombosis and at decreased risk for osteoporotic fractures. The global risk-benefit profile was neutral in the CEE treatment group, and the planned 8.5-year randomized clinical trial (RCT) was stopped after an average of 6.8 years of follow-up (range, 5.7-10.7 years). Although the parallel WHI trial of CEE and medroxyprogesterone acetate (CEE + MPA) and other results showed

that active treatment produced relief from vasomotor symptoms, the health-related quality of life (HRQOL) effects were limited to modest changes in physical functioning, sleep disturbance, and bodily pain that were considered too small to be of clinical significance on a population basis.[5-7]

The origin of the HRQOL concept has often been attributed to the World Health Organization position that health is a "state of complete physical, mental and social well-being and not merely the absence of infirmity and disease."[8] Health-related quality of life (QOL) limits the influences on QOL to medical conditions and/or their treatment.[9]

Typical self-assessment of HRQOL examines aspects of functioning that may relate to disease symptoms, disability, and outcome.[10] Many HRQOL instruments target symptoms for specific medical condi-

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tions.[11] However, the concept is also more broadly defined as encompassing multiple domains such as physical health and functioning, emotional functioning, social functioning, and role limitations.[12] This approach and a single summary measure, ie, "global" QOL, were used herein and in the earlier CEE + MPA RCT. They have been widely validated.[13-15] Quality-of-life benefit is a consideration in the decision to use hormone therapy.[16,17]

Several recent reports have found some domains of HRQOL to be affected by the transition from before to after menopause, with depressive symptoms tending not to be affected.[18-23] Women before the menopause transition compared with women who had begun the transition differed in reports of pain, role limitations, and vitality, but adjustments for symptoms (leaking urine, vaginal dryness, night sweats, and hot flashes) and other variables reduced differences in HRQOL to nonsignificance in a large cross-sectional study.[23,24] Estrogen alone as a postmenopausal hormone treatment continues to be offered for vasomotor symptom reduction, with collateral improvement reported in depression,[25] sexual functioning,[26] and cognitive functioning,[27] all of which are components of HRQOL and an influence on global QOL. However, objective evidence of efficacy, particularly from longitudinal studies of menopause[28] or randomized trials, have been inconsistent.[29,30] The present RCT is a randomized, double-blind, placebo-controlled study conducted in women with prior hysterectomy, which eliminates a major adverse effect of hormone therapy (uterine bleeding). Other adverse effects such as breast tenderness, bloating, and moodiness, which are sometimes attributed to the use of a progestin, also are reduced because progestin was not used in this study. Thus, the WHI CEE trial provides an excellent opportunity to evaluate HRQOL benefits of estrogen in a large, diverse population of relatively healthy, postmenopausal women, some with symptoms associated with estrogen therapy withdrawal and others nonsymptomatic.

METHODS

The eligibility criteria, recruitment procedures, and main study outcomes have been published previously.[4,31,32] Briefly, women aged 50 to 79 years with hysterectomy more than 3 months earlier (with or without oophorectomy) were potentially eligible for this RCT. Participation in the WHI was precluded if a medical condition predicted survival of less than 3 years or if there were diagnoses of previous breast cancer or melanoma, other cancer within the past 10 years (except nonmelanoma skin cancer), low hematocrit or platelet counts, or any condition that would interfere with acceptable adherence and retention (eg, alcoholism or dementia). A 3-month washout of any prevailing hormone therapy was required before starting data collection, screening, and enrollment. Women who reported moderate or severe menopausal symptoms during the washout period were not excluded but were discouraged from participating.

Initial consent forms, questionnaires, fasting blood draws, physical measurements, and breast and pelvic examinations were completed at 3 screening visits. As part of the screening process, women took placebo pills for at least 4 weeks to assess compliance with pill taking. Then, eligible participants were randomized to CEE (0.625 mg) or matching placebo treatment. Participants and clinic staff were blinded to the study pill

assignments. Clinic visits occurred 6 and 12 months (year 1 visit) after randomization, and annually thereafter. The baseline questionnaires were completed at the year 1 visit for all participants and, for an 8.6% subsample (n=1189), at the year 3 visit. The 8.6% subsample was selected to have a larger proportion of ethnic minority participants than the overall cohort. The National Institutes of Health, Bethesda, Md, and the institutional review boards of all participating institutions approved the protocol and consent forms.

ASSESSMENT OF HRQOL AND FUNCTIONAL STATUS

Quality of life/functional status was assessed using the RAND 36-Item Health Survey (RAND36).[33,34] The RAND36 has 8 subscales, each with a score range of 0 to 100 (with higher scores being better), that assess general health, physical functioning, role limitations due to physical health, bodily pain, energy and fatigue (vitality), role limitations due to emotional/mental problems, social functioning, and emotional/mental health and a stand-alone health transition question. Although the RAND36 contains the same items as the 36-item Medical Outcomes Study Short Form, it uses a slightly different scoring algorithm for 2 of the 8 subscales.

GLOBAL QOL

Global QOL was assessed by a single item ("Overall, how would you rate your quality of life?") with an 11-point response scale (0 indicates "as bad or worse than being dead" and 10, "best quality of life") that was reduced, for analysis, to 4 categories corresponding to poor (0-4), moderate (5-7), good (8), and excellent (9-10). The categories were chosen a priori and mirror those used in the Study of Women Across the Nation HRQOL.[23]

SLEEP QUALITY

Sleep quality was assessed by the 5-item Women's Health Initiative Insomnia Rating Scale that was developed and validated for use in the WHI.[35] Items in this survey referenced sleep during the past 4 weeks. Four items assessed sleep initiation and maintenance using a 5-point response scale (not in past 4 weeks; <1 time/wk; 1-2 times/wk; 3 or 4 times/wk; ≥5 times/ wk). A fifth item assessed sleep quality, also using a 5-point scale (very sound or restful, sound or restful, average quality, restless, and very restless). Scores ranged from 0 (worst) to 20 (best).

SEXUAL SATISFACTION

Sexual satisfaction ("How satisfied are you with your current sexual activities, either with a partner or alone?") was assessed by a single item with a 4-point response scale (very unsatisfied, a little unsatisfied, somewhat satisfied, or very satisfied). Scores ranged from 1 (worst) to 4 (best).

COGNITIVE FUNCTIONING

Cognitive functioning was assessed in participants 65 years or older by the Modified Mini-Mental State Examination,[36] a scale used in the Cardiovascular Health Study.[37] The Modified Mini-Mental State Examination has 15 parts with 46 separately scored items. Maximum (best) scores per item range from 1 to 8 (with a total of 100). The functions tested are orientation to time, place, and person; short-term memory; reading; writing; naming; verbal fluency; praxis; and graphomotor performance.

DEPRESSIVE SYMPTOMS

Depressive symptoms were assessed by means of an 8-item scale[38] developed to screen for depressive disorders (major depression and dysthymia). It included 6 items from the Center for Epidemiological Studies Depression Scale[39] and 2 items from the Diagnostic Interview Schedule.[40] Scores may range from –8.2 (best) to 4.0 (worst). In this questionnaire, a lower score is desirable.

STATISTICAL ANALYSES

All primary analyses focused on changes in HRQOL from baseline to year 1 in relation to CEE randomization assignment. For each of the 13 HRQOL measures, we fit a linear model to test whether CEE had a significant treatment effect on HRQOL change score. To examine whether the CEE effect was moderated by baseline variables, we fit a series of linear models. Each pair, a baseline variable and the corresponding CEE interaction, was added one at a time, followed by a test of the interaction. Baseline characteristics included age, body mass index, ethnicity, moderate or severe vasomotor symptoms, previous hormone therapy use, years since menopause, bilateral oophorectomy status, history of cardiovascular disease, and socioeconomic variables (education, income, and health insurance status). Menopause was defined as the lowest age according to last menses, age at bilateral oophorectomy, or age when hormone therapy was started. If the ovaries were partially removed/intact, menopause was defined as the lower of the age hormone therapy was started or the age at first menopausal symptoms. Similar analyses were performed on data available at year 3 for the 8.6% subsample.

Statistical significance of the effect of CEE on HRQOL and of the tests of interactions were judged by Bonferroni-corrected αs of 0.005 (0.05/13, approximately 0.005) and 0.0005 (approximately 0.05/[13 × 11]), respectively. Actual *P* values, unadjusted for multiple comparison, are reported exclusively throughout the text and tables.

A post hoc analysis examined participants aged 50 to 54 years who reported moderate to severe night sweats or hot flashes at baseline. Because *P* values of treatment effects from subgroups can be misleading,[41] we did not use a Bonferroni-adjusted α level for this analysis and caution readers to carefully interpret their values. All analyses were based on the intention-to-treat principle using SAS version 9.1.[42]

RESULTS

Overall, 5310 women were randomized into the CEE group and 5429 into the placebo group. The intervention groups were balanced on key demographic characteristics except for a slight statistical difference in bilateral oophorectomy status (**Table 1**). There were 2.5% fewer women in the CEE group with bilateral oophorectomy than in the placebo group. The mean age in the cohort was 63.6 years; 75.3% were white; 23.9% had a college education; 48.4% had some previous hormone use; and 17.3% had moderate/severe vasomotor symptoms at baseline. Baseline scores on the RAND36 were similar to scores observed in other healthy populations.[43] The scores were somewhat lower than those seen in the WHI CEE + MPA trial among women with a uterus.[5]

This analysis focused on changes in HRQOL measures during the first year of taking study drugs. At year 1, vital status was known for 100% of participants, in-

cluding the 0.4% who died, and none were lost to follow-up. During the first year, study therapy was stopped for various reasons by 8.4% of women randomized to CEE and 8.0% of women randomized to placebo. Overall, 78% of women randomized to CEE and 82% of women randomized to placebo were adherent (defined as taking ≥80% of pills) at year 1. At year 3, in the subsample, adherence was 59% for both treatment groups.

In examining the change in HRQOL measures from baseline to year 1, few differences were observed between the CEE and placebo groups (**Table 2**). There was a small (0.40 difference on the 20-point scale) but statistically significant positive effect of CEE, relative to placebo, on sleep disturbance (*P*<.001). Based on Cohen's[44] rule of thumb, the effect size on sleep (0.4/3.88=0.1) does not even achieve the threshold for a small (≥0.2) effect size. There was also a small but statistically significant negative effect of CEE on social functioning (*P*=.003). At year 1, there were no other HRQOL variables for which a clinically meaningful or statistically significant improvement was observed with CEE.

Differences from baseline to year 1 in the approximately 8.6% random subsample of women whose measures were repeated at year 3 (n=577 in the CEE group; n=612 in the placebo group) are displayed in **Table 3**. Treatment with CEE did not produce a statistically significant improvement in any HRQOL variables at year 1 or year 3 in this subsample. Further analyses explored whether there were substantive effects of CEE on HRQOL that depended on demographic, health, or other measures taken at baseline. There were no significant interactions of intervention assignment and any of the following: age, race/ethnicity, education, income, insurance status, body mass index, vasomotor symptoms (moderate or severe night sweats/hot flashes), years since menopause, previous use of any type of hormone therapy, bilateral oophorectomy status, or history of cardiovascular disease. Analyses of the following 3 subgroups were of particular interest: (1) women who had undergone bilateral oophorectomy, (2) women who reported moderate or severe vasomotor symptoms at baseline (hot flashes or night sweats), and (3) the youngest age group (with symptoms). These subgroups may have experienced greater improvements in QOL from relief of symptoms by CEE. There was no significant difference in the effect of CEE on HRQOL among women who had undergone bilateral oophorectomy compared with those who had not. Apart from HRQOL, we examined the effects of CEE on relief of symptoms specifically among women who reported moderate or severe vasomotor symptoms at baseline (913 women in the CEE and 917 in the placebo groups). At the 1-year follow-up, 72.4% of women reporting moderate or severe vasomotor symptoms at baseline in the CEE group no longer reported them, compared with 55.6% of women in the placebo group (*P*<.001). As shown in **Table 4**, an additional restriction to women aged 50 to 54 years reporting moderate or severe vasomotor symptoms at baseline does not magnify any positive effect of CEE on HRQOL variables. For 7 of the 13 HRQOL changes (baseline to year 1), these youngest participants in the CEE group had worse scores than the placebo group. A higher proportion of participants in the placebo group (39%) reported, at year 1, much

Table 1. Baseline Characteristics by Treatment Assignment (Missing Excluded)

Characteristic	Treatment, No. (%)		P Value
	CEE Group	Placebo Group	
Age at screening, y			
50-54	687 (12.9)	709 (13.1)	
55-59	950 (17.9)	964 (17.8)	
60-69	2387 (45.0)	2465 (45.4)	.94
70-79	1286 (24.2)	1291 (23.8)	
Ethnicity			
White	4007 (75.5)	4075 (75.1)	
Black	782 (14.7)	835 (15.4)	
Hispanic	322 (6.1)	333 (6.1)	
American Indian	41 (0.8)	34 (0.6)	.81
Asian/Pacific Islander	86 (1.6)	78 (1.4)	
Unknown	72 (1.4)	74 (1.4)	
BMI (collapsed categories)			
<25	1110 (21.0)	1096 (20.3)	
25-<30	1795 (34.0)	1912 (35.5)	.26
≥30	2376 (45.0)	2383 (44.2)	
Education			
0-8 y	181 (3.4)	148 (2.7)	
Some high school	354 (6.7)	370 (6.9)	
High school diploma/GED	1233 (23.5)	1188 (22.1)	.06
School after high school	2271 (43.2)	2350 (43.7)	
College degree or higher	1216 (23.1)	1327 (24.7)	
Annual family income, $			
<10 000	423 (8.4)	441 (8.6)	
10 000-19 999	999 (19.9)	990 (19.4)	
20 000-34 999	1492 (29.8)	1507 (29.5)	
35 000-49 999	947 (18.9)	1000 (19.6)	.90
50 000-74 999	725 (14.5)	722 (14.1)	
≥75 000	422 (8.4)	444 (8.7)	
Age at hysterectomy, y			
<40	2100 (39.8)	2149 (39.8)	
40-49	2281 (43.2)	2275 (42.2)	.34
50-54	501 (9.5)	566 (10.5)	
≥55	401 (7.6)	404 (7.5)	
Years since menopause			
<5	330 (7.3)	325 (7.0)	
5 to <10	496 (11.0)	492 (10.6)	.83
10 to <15	704 (15.7)	734 (15.8)	
≥15	2963 (65.9)	3085 (66.5)	
Duration of previous hormone use, y			
0	2769 (52.1)	2770 (51.0)	
<5	1352 (25.5)	1412 (26.0)	.53
5 to <10	469 (8.8)	515 (9.5)	
≥10	720 (13.6)	732 (13.5)	
Baseline moderate/severe vasomotor symptoms			
No	4327 (82.6)	4431 (82.9)	.71
Yes	913 (17.4)	917 (17.1)	
History of CVD			
No	4768 (90.9)	4893 (91.3)	.53
Yes	477 (9.1)	469 (8.7)	
Prior bilateral oophorectomy			
No	2973 (60.5)	2917 (58.0)	.01
Yes	1938 (39.5)	2111 (42.0)	

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters); CEE, conjugated equine estrogen; CVD, cardiovascular disease; GED, General Educational Development test.

better or somewhat better health than participants in the CEE group (23%) (**Table 5**).

The single global item asked: "Overall, how would you rate your quality of life?" The distributions of global scores did not differ between the CEE and placebo groups (data not shown). In both groups, less than 3% reported poor and 40% reported excellent global QOL. The CEE and placebo groups were very similar in the proportions of participants who rated their global QOL in the moderate and good categories (26%-30%). **Table 6** offers a sense of the

Table 2. Change in QOL Scores From Baseline to Year 1

Variable	CEE Group		Placebo Group		Difference	
	No. of Subjects	Mean (SD) Score	No. of Subjects	Mean (SD) Score	Mean (SE)	P Value
General health*						
Baseline	5210	71.95 (17.97)	5334	72.38 (18.05)	−0.43 (0.35)	.22
Year 1	4654	−0.31 (13.71)	4767	−0.37 (14.24)	0.07 (0.29)	.82
Physical functioning*						
Baseline	5185	76.47 (21.98)	5297	77.23 (21.76)	−0.77 (0.43)	.07
Year 1	4580	−1.20 (15.57)	4678	−1.89 (15.81)	0.69 (0.33)	.04
Role physical*						
Baseline	5226	70.49 (36.75)	5356	70.22 (36.94)	0.27 (0.72)	.70
Year 1	4664	−2.04 (38.30)	4783	−1.81 (38.58)	−0.23 (0.79)	.77
Bodily pain*						
Baseline	5251	70.67 (24.65)	5384	70.75 (24.85)	−0.08 (0.48)	.87
Year 1	4764	−1.22 (22.76)	4885	−1.98 (22.94)	0.76 (0.47)	.11
Vitality*						
Baseline	5217	60.55 (20.00)	5324	61.04 (20.23)	−0.49 (0.39)	.21
Year 1	4662	−0.14 (16.04)	4757	−0.02 (16.36)	−0.12 (0.33)	.72
Social functioning*						
Baseline	5245	88.61 (18.76)	5366	88.10 (19.47)	0.51 (0.37)	.17
Year 1	4736	−3.09 (21.98)	4836	−1.77 (21.75)	−1.31 (0.45)	.003†
Role emotional*						
Baseline	5242	81.56 (31.89)	5366	82.17 (31.12)	−0.61 (0.61)	.32
Year 1	4682	−1.56 (33.99)	4801	−0.43 (33.63)	−1.13 (0.69)	.10
Mental health*						
Baseline	5220	77.37 (15.58)	5335	77.90 (15.26)	−0.54 (0.30)	.08
Year 1	4651	0.60 (13.28)	4750	0.56 (13.32)	0.03 (0.27)	.91
Depressive symptoms‡						
Baseline	5103	−5.21 (2.08)	5231	−5.24 (2.06)	0.03 (0.04)	.51
Year 1	4465	−0.17 (1.93)	4599	−0.13 (1.91)	−0.04 (0.04)	.33
3MSE*						
Baseline	1784	94.28 (5.02)	1788	94.33 (5.13)	−0.05 (0.17)	.77
Year 1	1637	0.47 (6.45)	1648	0.87 (4.14)	−0.39 (0.19)	.04
Sleep disturbance§						
Baseline	5178	12.54 (4.76)	5284	12.71 (4.73)	−0.17 (0.09)	.07
Year 1	4574	0.46 (3.84)	4670	0.07 (3.88)	0.40 (0.08)	<.001†
Satisfaction with sex‖						
Baseline	4206	2.91 (1.10)	4256	2.93 (1.09)	−0.02 (0.02)	.43
Year 1	3314	0.01 (1.13)	3368	0.02 (1.12)	−0.01 (0.03)	.65

Abbreviations: CEE, conjugated equine estrogen; 3MSE, Modified Mini-Mental State Examination; QOL, quality of life.
*Scored from 0 (worst) to 100 (best).
†P value is statistically significant at Bonferroni corrected α level of 0.005; in all tables actual, unadjusted P values are presented.
‡Scored from 4.0 (worst) to −8.1 (best).
§Scored from 0 (worst) to 20 (best).
‖Scored from 0 (worst) to 4 (best).

metric for HRQOL (eg, RAND36 scores) by showing differences that are associated with categorical increments in global QOL. As examples, the HRQOL mean scores were approximately 1 SD higher for women who rated their global QOL as excellent compared with those who rated it as moderate. The HRQOL sleep disturbance score was 3 points higher (less disturbance) for women rating their global QOL as excellent compared with those rating it as moderate. Higher ratings of global QOL were associated with higher scores on each of the RAND36 subscales and lower scores on the depression measures, all suggesting that this global item is sensitive to symptoms and functioning. Also, regardless of treatment assignment, moderate to severe menopausal symptoms and adverse effects of hormone therapy were significantly associated with worse global QOL.

Because of the slight imbalance of bilateral oophorectomy status by treatment assignment, we performed a sensitivity analysis of our primary results. Adjustment of bilateral oophorectomy status did not change conclusions regarding sleep disturbance; the mean difference between the CEE and placebo groups changed from 0.40 to 0.38 and remained statistically significant ($P \leq .001$). However, oophorectomy adjustment slightly attenuated the effect of CEE on social functioning; after adjustment, the mean difference changed from −1.31 to −1.16 ($P = .01$) and consequently did not reach the Bonferroni-corrected α level. None of the other results were changed after adjusting for bilateral oophorectomy status.

COMMENT

In the WHI RCT of CEE alone,[4] a clinically meaningful benefit of CEE treatment on HRQOL was not found in

Table 3. Change in QOL Scores at Years 1 and 3 Compared With Baseline in CEE Subgroup of 1189 Participants

Variable	CEE Group		Placebo Group		Difference	
	No. of Subjects	Mean (SD) Score	No. of Subjects	Mean (SD) Score	Mean (SE)	P Value
General health*						
Baseline	559	71.06 (18.61)	596	71.38 (17.74)	−0.33 (1.07)	.76
Year 1	488	−1.88 (14.89)	519	−0.47 (14.53)	−1.40 (0.93)	.13
Year 3	475	−3.51 (14.85)	487	−2.90 (15.12)	−0.61 (0.97)	.53
Physical functioning*						
Baseline	554	75.60 (22.87)	593	77.56 (20.89)	−1.97 (1.29)	.13
Year 1	475	−1.65 (16.35)	513	−2.72 (16.75)	1.07 (1.05)	.31
Year 3	456	−4.67 (18.91)	483	−6.21 (19.08)	1.54 (1.24)	.22
Role physical*						
Baseline	563	68.83 (36.75)	602	70.02 (37.08)	−1.19 (2.16)	.58
Year 1	492	−2.29 (40.69)	527	−1.42 (40.35)	−0.86 (2.54)	.73
Year 3	476	−5.78 (40.69)	490	−6.73 (42.19)	0.96 (2.67)	.72
Bodily pain*						
Baseline	563	70.71 (24.74)	606	70.75 (24.79)	−0.04 (1.45)	.98
Year 1	505	−1.51 (24.04)	538	−2.37 (24.12)	0.86 (1.49)	.56
Year 3	479	−4.62 (24.33)	500	−5.33 (25.37)	0.71 (1.59)	.66
Vitality*						
Baseline	558	60.08 (19.89)	593	60.95 (20.55)	−0.87 (1.19)	.47
Year 1	484	−0.59 (15.41)	516	0.66 (17.26)	−1.25 (1.04)	.23
Year 3	471	−1.28 (16.36)	483	−2.26 (18.54)	0.97 (1.13)	.39
Social functioning*						
Baseline	562	88.19 (18.67)	604	87.44 (19.55)	0.75 (1.12)	.50
Year 1	499	−3.83 (23.66)	534	−1.73 (22.14)	−2.10 (1.42)	.14
Year 3	476	−4.86 (23.59)	501	−3.62 (23.29)	−1.24 (1.50)	.41
Role emotional*						
Baseline	567	78.31 (33.36)	602	79.84 (32.35)	−1.54 (1.92)	.42
Year 1	494	−2.16 (37.32)	526	0.25 (33.68)	−2.41 (2.22)	.28
Year 3	478	−1.74 (37.75)	496	−3.90 (39.16)	2.15 (2.47)	.38
Mental health*						
Baseline	559	77.14 (15.93)	597	77.09 (15.31)	0.05 (0.92)	.96
Year 1	487	−0.34 (13.11)	522	0.90 (13.93)	−1.25 (0.85)	.14
Year 3	472	−0.45 (14.76)	483	0.17 (14.74)	−0.61 (0.95)	.52
Depressive symptoms†						
Baseline	545	−5.18 (2.06)	579	−5.29 (2.01)	0.11 (0.12)	.36
Year 1	460	−0.18 (2.09)	498	0.03 (1.93)	−0.21 (0.13)	.11
Year 3	453	−0.10 (2.09)	464	−0.06 (2.17)	−0.04 (0.14)	.77
3MSE*						
Baseline	194	93.07 (5.09)	200	92.70 (5.49)	0.37 (0.53)	.49
Year 1	180	0.67 (8.56)	177	0.97 (3.99)	−0.30 (0.71)	.67
Year 3	172	1.52 (4.18)	166	1.30 (5.01)	0.23 (0.50)	.65
Sleep disturbance‡						
Baseline	561	12.96 (4.72)	592	12.97 (4.71)	−0.02 (0.28)	.96
Year 1	489	0.18 (3.89)	517	0.00 (4.00)	0.18 (0.25)	.47
Year 3	464	0.00 (4.32)	480	−0.20 (4.22)	0.20 (0.28)	.48
Satisfaction with sex§						
Baseline	456	2.89 (1.11)	453	2.80 (1.13)	0.09 (0.07)	.21
Year 1	354	−0.07 (1.19)	348	0.07 (1.07)	−0.15 (0.09)	.09
Year 3	324	0.01 (1.22)	325	0.04 (1.18)	−0.03 (0.09)	.74

Abbreviations: CEE, conjugated equine estrogen; 3MSE, Modified Mini-Mental State Examination; QOL, quality of life.
*Scored from 0 (worst) to 100 (best).
†Scored from 4.0 (worst) to −8.1 (best).
‡Scored from 0 (worst) to 20 (best).
§Scored from 0 (worst) to 4 (best).

an ethnically diverse population of postmenopausal women who had undergone hysterectomy before entering the study. Failure to demonstrate global improvement in HRQOL occurred, despite absence of uterine bleeding or other progestin-associated adverse effects.

These results were similar to results reported for women with a uterus in the WHI CEE + MPA trial.[5] In both trials, a statistically significant, small improvement in average sleep disturbance score was found after 1 year of hormone treatment. Women with vasomotor symptoms experienced a significant decline in these symptoms, but the positive effects on physical functioning and bodily pain seen in the WHI CEE + MPA trial were not found here.

Table 4. Changes in QOL Scores From Baseline to Year 1 Among Subjects Aged 50 to 54 Years With Moderate or Severe Vasomotor Symptoms

	CEE Group		Placebo Group		Difference	
Subscale	No. of Subjects	Mean (SD) Score	No. of Subjects	Mean (SD) Score	Mean (SE)	P Value
General health*	162	−0.52 (14.87)	162	1.82 (15.47)	−2.35 (1.69)	.17
Physical functioning*	165	−0.61 (17.21)	156	−0.51 (21.37)	−0.09 (2.16)	.97
Role physical*	167	−1.35 (40.07)	163	2.91 (40.96)	−4.26 (4.46)	.34
Bodily pain*	169	−4.36 (24.93)	165	0.45 (26.00)	−4.82 (2.79)	.09
Vitality*	166	1.23 (18.73)	161	0.84 (18.94)	0.40 (2.08)	.85
Social functioning*	167	−2.17 (26.99)	165	0.45 (23.14)	−2.63 (2.76)	.34
Role emotional*	167	1.00 (36.30)	164	0.41 (38.01)	0.59 (4.08)	.89
Mental health*	167	1.08 (16.50)	163	0.59 (15.96)	0.49 (1.79)	.79
Depressive symptoms†	159	−0.15 (2.63)	151	0.08 (2.59)	−0.23 (0.30)	.44
Sleep disturbance‡	165	1.35 (4.60)	157	0.53 (4.59)	0.82 (0.51)	.11
Satisfaction with sex§	140	−0.07 (1.12)	134	0.02 (1.17)	−0.09 (0.14)	.50

Abbreviations: CEE, conjugated equine estrogen; QOL, quality of life.
*Scored from 0 (worst) to 100 (best).
†Scored from 4.0 (worst) to −8.1 (best).
‡Scored from 0 (worst) to 20 (best).
§Scored from 0 (worst) to 4 (best).

Table 5. Change in Rating of General Health*

	Overall†		Subjects Aged 50-54 Years With Moderate/Severe Vasomotor Symptoms†	
Response	CEE Group	Placebo Group	CEE Group	Placebo Group
Much better now	368 (7.6)	323 (6.6)	9 (5.2)	21 (12.7)
Somewhat better now	754 (15.6)	738 (15.0)	31 (18.0)	43 (25.9)
About the same	3075 (63.7)	3156 (64.3)	104 (60.5)	76 (45.8)
Somewhat worse now	589 (12.2)	646 (13.2)	25 (14.5)	24 (14.5)
Much worse now	38 (0.8)	47 (1.0)	3 (1.7)	2 (1.2)

Abbreviation: CEE, conjugated equine estrogen.
*Indicates answers to the question "Compared to 1 year ago, how would you rate your general health now?" Excludes missing subjects. Data are given as number (percentage). Percentages have been rounded and may not total 100.
†$P<.01$ between treatment groups, based on 2-sided Cochran-Armitage test for trend to determine whether active treatment is associated with an increasing or decreasing health-related quality of life at year 1.

Several baseline differences in HRQOL were noted between women in the CEE + MPA trial (with a uterus) and women in the CEE trial (without a uterus). The average bodily pain score at baseline was significantly more negative (more pain) in the CEE trial than in the CEE + MPA trial ($P \leq .001$). Similarly, women in the CEE trial had worse physical functioning scores at baseline ($P \leq .001$). Also, in the CEE + MPA trial, at baseline, fewer women reported poor and more reported excellent global QOL than in the present trial ($P<.001$). However, after 1 year, the CEE and CEE + MPA groups did not differ from their respective placebo groups in global QOL. The subsample with HRQOL undergoing reassessment 3 years from baseline provided no evidence that longer-term use of CEE improves HRQOL measures compared with a shorter-term use. It could be argued that the limited effects of CEE on HRQOL resulted from a too conservative α level probability threshold, one that had been adjusted for multiple comparisons. However, we have presented actual (unadjusted) P values, so the reader may

decide what they consider statistically significant. For example, applying a liberal α value of .05 would only add a statistically significant improvement in physical functioning from CEE, which then is perhaps offset by a significant negative change in cognitive functioning.

The minimal benefit of CEE on HRQOL (2% improvement in sleep disturbance symptoms) does not challenge the current treatment guidelines. The findings suggest that asymptomatic women using estrogen therapy, eg, for prevention of osteoporosis, are unlikely in the short term to experience a meaningful improvement in HRQOL.

Overall, our results are consistent with other recent randomized trials[46,47] and epidemiological studies.[48] The WHI and other studies indicate that some menopausal vasomotor symptoms improve with estrogen treatment. There is little or no benefit of systemic hormone treatment for most other physical, functional, and psychosocial conditions, with some, like nocturnal urinary frequency, worsening.[49,50] The HRQOL measures may be considered subjective aggregates that are complexly influenced by the combination of

Table 6. Relationship of Vasomotor Symptoms, Adverse Effects of Treatment, and RAND36 Scores to Global QOL at Year 1 Collapsed by Treatment Assignment

	Global QOL Rating at Year 1			
Variable	Poor (n = 235)	Moderate (n = 2671)	Good (n = 2884)	Excellent (n = 3944)
Events through year 1, No. (%) of subjects*†	2 (0.9)	40 (1.5)	26 (0.9)	24 (0.6)
Prevalence of moderate/severe symptoms at year 1‡				
Vasomotor symptoms§	66 (29.1)	428 (16.2)	265 (9.3)	293 (7.5)
Vaginal dryness	32 (13.9)	283 (10.8)	221 (7.7)	258 (6.6)
General aches and pains	160 (69.6)	1265 (47.9)	916 (32.1)	708 (18.1)
Joint pain and stiffness	150 (64.7)	1225 (46.6)	941 (32.9)	820 (20.9)
Prevalence of moderate/severe adverse effects at year 1‖				
Breast tenderness	28 (12.2)	242 (9.1)	177 (6.2)	209 (5.3)
Vaginal discharge	8 (3.5)	75 (2.8)	62 (2.2)	58 (1.5)
Vaginal itch	22 (9.5)	226 (8.6)	153 (5.3)	171 (4.4)
Headache	63 (27.4)	476 (18.0)	327 (11.4)	352 (9.0)
Other HRQOL variables, mean (SD) scores¶				
General health	48.0 (21.0)	61.3 (18.3)	72.3 (15.4)	80.8 (14.9)
Physical functioning	51.7 (30.6)	65.5 (26.1)	76.6 (21.1)	83.0 (18.8)
Role physical	33.5 (37.4)	52.5 (41.1)	69.5 (37.3)	81.8 (31.0)
Bodily pain	43.6 (28.8)	58.5 (27.0)	69.7 (23.4)	78.3 (21.5)
Vitality	27.2 (20.0)	48.3 (20.0)	61.1 (17.9)	71.5 (16.3)
Social functioning	52.7 (28.5)	75.9 (24.4)	88.5 (18.3)	93.8 (14.2)
Role emotional	40.1 (38.5)	67.4 (38.5)	85.2 (28.5)	91.0 (23.1)
Mental health	49.5 (19.2)	68.6 (16.8)	79.9 (12.4)	86.2 (10.9)
Depressive symptoms	−2.2 (2.8)	−4.5 (2.4)	−5.6 (1.6)	−6.1 (1.3)
3MSE	93.7 (14.0)	94.1 (7.0)	95.3 (4.6)	95.2 (5.2)
Sleep disturbance	9.9 (5.4)	11.3 (4.9)	12.9 (4.5)	14.3 (4.3)
Satisfaction with sex	2.4 (1.1)	2.7 (1.1)	3.0 (1.0)	3.1 (1.1)

Abbreviations: HRQOL, health-related QOL; 3MSE, Modified Mini-Mental State Examination; QOL, quality of life; RAND36, RAND 36-Item Health Survey.

*Includes myocardial infarction, hip fracture, invasive breast cancer, colon cancer, stroke, and pulmonary embolism before their year 1 QOL data were collected.

†$P<.001$ based on 1-sided Cochran-Armitage test for linear trend to test whether higher prevalence of symptoms and higher incidence of events are associated with lower global QOL.

‡These symptoms were identified a priori and are based on the Women's Health Initiative conjugated estrogen and medroxyprogesterone acetate gynecological symptoms data).[45]

§Includes hot flashes and/or night sweats.

‖These effects were identified a priori based on the Women's Health Initiative conjugated estrogen and medroxyprogesterone acetate gynecological symptoms data.[45]

¶$P<.001$ based on 1-sided test for linear trend to determine whether higher HRQOL scores are associated with higher global QOL scores.

estrogen replacement's improvement in vasomotor symptoms (and/or other unspecified positive effects), adverse effects, and consequences for disease processes and end points. Part of the rationale for the original study design was that estrogen would have health benefits (bone, heart, and cognition) that would be reflected in HRQOL measures. The absence of an improvement with estrogen in the global index, the study's overall risk-benefit health profile,[4] may help explain the weak response of HRQOL measures.

As a randomized clinical trial of relatively healthy women after menopause, it might be argued that the potential for positive health differences was limited by a "ceiling" that effectively reduced the range of scores at the upper end of the spectrum. This may be the case for the 2-item social functioning subscale (mean score lower in the CEE group) of the RAND36, which has a coarse Likert scale. Most participants attained the maximum score on social functioning. For other subscales, average scores were well below the possible maximum. For example, only 1% of subjects had maximum vitality scores, and baseline HRQOL scores were generally lower in this population than in the previously reported

CEE + MPA trial in women without a hysterectomy. We attribute the latter difference largely to more health risk factors and lower socioeconomic status in the women with hysterectomy.

Some reports suggest that estrogen therapy might play a role in the management of severe emotional and mental changes in the postpartum or perimenopausal periods.[51,52] The impact of estrogen treatment in clinical mood disorders may be very different than its population effects in healthy women not selected for such disturbances.

Estrogen therapy alone in women with a hysterectomy did not produce clinically meaningful improvements in HRQOL measures compared with placebo, despite reduction of some vasomotor symptoms resulting from the active treatment, albeit in the relatively small proportion of women in the cohort who were symptomatic. Any overall impact may have been lessened by the size of the specific effect on sleep disturbance, which, as one of the more widely reported and enduring problems in this age group, had only a small average improvement, perhaps because nocturnal urinary frequency may worsen with hormone treatment.[49] Moreover, recent reviews have suggested that subjectively reported sleep dis-

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turbance during and after menopause has multiple causes and that its relationship to hormone changes is complex.[53,54] In the WHI, health risks and benefits were relatively balanced after more than 6 years of CEE use. Individual women may experience some improvement in their vasomotor and urogenital atrophy symptoms, but these may be partly offset by adverse effects associated with postmenopausal hormone treatment. We find no evidence of an HRQOL benefit for the general postmenopausal population.

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